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Boric acid as a mild and efficient catalyst for one-pot synthesis of 1-amidoalkyl-2-naphthols under solvent-free conditions

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Abstract. An efficient green chemistry method has been developed for the synthesis of 1-amidoalkyl-2-naphthol derivatives via a one-pot three-component condensation of 2-naphthol, aldehydes and amide in the presence of boric acid as a mild catalyst.

Keywords. Multicomponent reaction; amidoalkyl naphthol; boric acid; catalyst; solvent-free synthesis.

1. Introduction

Multicomponent reactions (MCRs), in which three or more reactants are combined in a one-pot process, have become an efficient and powerful tool for the construction of complex molecules.[1] In recent years, MCRs have attracted extensive efforts by researchers in modern synthetic chemistry because they increase the efficiency by combining several operational steps without the isolation of intermediates or changing the reaction conditions. The development and application of MCRs are now an integral part of the work of any major medical research unit.[2]

1-Amidoalkyl-2-naphthol derivatives are of significant medical relevance since they can be converted into hypertensive and bradycardia active 1-aminoalkyl-2-naphthols by amide hydrolysis reaction.[3] The preparation of amidoalkyl naphthols can be carried out by multicomponent condensation of aldehydes, 2-naphthol and amides in the presence of Lewis or Brønsted acid catalysts such as montmorillonite K10 clay,[4] $Ce(SO_4)_2$,[5] $K_5CoW_{12}O_{40}\cdot 3H_2O$,[6] iodine,[7] $ZrOCl_2\cdot 8H_2O$,[8] sulphamic acid,[9] silica-supported perchloric acid,[10] $Fe(HSO_4)_3$,[11] P_2O_5,[12] $FeCl_3\cdot SiO_2$,[13] silica-sodium hydrogen sulphate,[14] molybdophosphoric acid ($H_3[P(Mo_3O_{10})_4]$),[15] *p*-toluenesulphonic acid,[16] $H_3PW_{12}O_{40}$,[17] silicotungstic acid ($H_4SiW_{12}O_{40}$),[18] wet cyanuric chloride,[19] perchloric acid supported on alumina (Al_2O_3-$HClO_4$),[20] *N,N,N′,N′*–tetrabromobenzene-1,3-disulphonamide [TBBDA],[21] trityl chloride,[22] Cu-exchanged heteropoly acids,[23] cation-exchange resins,[24] silica chloride,[25] Hafnium (IV) bis(perfluorooctanesulphonyl)imide complex,[26] copper *p*-toluenesulphonate,[27] 2,4,6-trichloro-1,3,5-triazine,[28] Zeolite,[29] Indium chloride,[30] zinc benzenesulphonate[31] and ionic liquids.[32] However, some of the reported methods suffer from disadvantages such as long reaction time, the use of toxic, corrosive, expensive or non-reusable catalysts, low yields of products, the use of large amount of catalyst and strongly acidic conditions. Therefore, to overcome these limitations, the discovery of a new, inexpensive, easily available catalyst with high catalytic activity and short reaction time for the preparation of amidoalkyl naphthols is essential.

In recent years, boric acid has been used in organic synthesis because it is commercially available, environmentally benign, cheap, easy to handle, and stable. Boric acid has been utilized in numerous reactions, for example, aza-Michael[33] and thia-Michael reactions,[34] transesterification of ethyl acetoacetate,[35] preparation of α-hydroxyamides,[36] oxidation of sulphides,[37] Biginelli reaction,[38] synthesis of 1,5-benzodiazepine derivatives,[39] and synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines.[40] It is therefore of interest to examine the behaviour of boric acid as catalyst in the synthesis of amidoalkyl naphthols. In this work, we describe a new and convenient synthesis of amidoalkyl naphthols by multicomponent reaction of 2-naphthol, aromatic aldehydes and acetamide catalysed by boric acid under solvent-free conditions (scheme 1).

2. Experimental

All chemicals were purchased from Merck and Fluka Chemical Companies. Melting points were determined on a MEL-TEMP model 1202D and are uncorrected.

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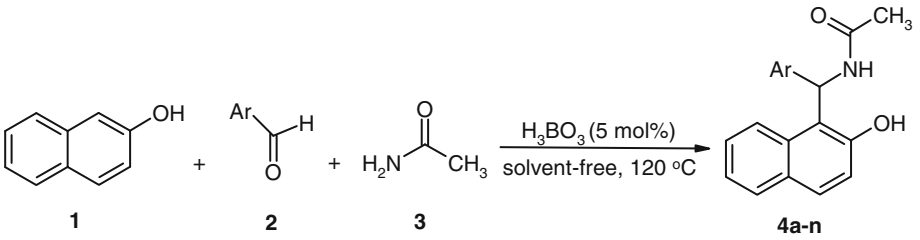


Scheme 1. Synthesis of 1-amidoalkyl-2-naphthols using boric acid.

FT-IR spectra were recorded on a Bruker Tensor 27 spectrometer as KBr disks. The ^{1}H NMR spectra were recorded with a Bruker Spectrospin Avance 400 spectrometer. ^{13}C NMR spectra were determined on the same instrument at 100 MHz. All chemical shifts are reported in δ (ppm) relative to solvent peaks as an internal standard and coupling constants (J) are given in Hz.

2.1 *General procedure for the synthesis of amidoalkyl naphthols*

To a mixture of aldehyde (1 mmol), 2-naphthol (1 mmol) and acetamide (1.2 mmol) boric acid (5 mol%) was added. The mixture was stirred at 120°C in an oil bath and the completion of reaction was monitored by TLC (acetone/*n*-hexane: 1/3). After completion of the reaction, the mixture was cooled to room temperature, and water (10 ml) was added, and the mixture was stirred for 10 min. The solid obtained was collected by filtration and purified by recrystallization from ethanol.

2.2 *Spectral data of selected products*

2.2a *N-[(2-Hydroxynaphthalen-1-yl)(4-chlorophenyl) methyl]acetamide*(**4d**): Pale yellow solid; mp 236–238°C (lit.[12] mp 237–238°C); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ (ppm) 1.99 (s, 3H), 7.11 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 8.3 Hz, 2H), 7.22–7.28 (m, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.37 (t, J = 6.9 Hz, 1H), 7.76–7.81 (m, 3H), 8.50 (d, J = 8.1 Hz, 1H), 10.09 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): 22.3, 47.1, 118.1, 118.2, 122.2, 122.8, 126.2, 127.6, 127.7, 128.2, 128.3, 129.2, 130.4, 131.9, 141.5, 152.9, 169.2 ppm; FT-IR (KBr, cm^{-1}): 3387, 2963, 1629, 1519, 1434, 1081, 809, 748.

2.2b *N-[(2-Hydroxynaphthalen-1-yl)(3-bromophenyl) methyl]acetamide*(**4f**): White solid; mp 229–230°C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ (ppm) 1.99 (s, 3H), 7.08–7.42 (m, 8H), 7.74–7.83 (m, 3H), 8.52 (d, J = 8.2 Hz, 1H), 10.09 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): 22.6, 47.4, 118.2, 118.4, 121.5, 122.5, 122.9, 125.2, 126.6, 128.4, 128.5, 128.6, 128.9, 129.6, 130.0, 132.2, 145.7, 153.2, 169.5 ppm; FT-IR (KBr, cm^{-1}): 3408, 3062, 1639, 1509, 1434, 1065, 807, 749; Anal. Calcd. for $C_{19}H_{16}BrNO_2$%: C: 61.64, H: 4.36, N: 3.78. Found: C: 61.32, H: 4.45, N: 3.71%.

2.2c *N-[(2-Hydroxynaphthalen-1-yl)(thiophen-2-yl) methyl]acetamide*(**4l**): Pale yellow solid; mp 224–225°C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ (ppm) 1.94 (s, 3H), 6.73 (d, J = 2.7 Hz, 1H), 6.87–6.89 (m, 1H), 7.21–7.31 (m, 4H), 7.39 (t, J = 6.7 Hz, 1H), 7.76–7.82 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 8.64 (d, J = 8.0 Hz, 1H), 10.17 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): 21.3, 43.7, 117.0, 117.1, 121.2, 121.8, 122.7, 123.1, 125.1, 125.3, 127.1, 127.3, 128.3, 130.7, 145.7, 151.8, 167.7 ppm; FT-IR (KBr, cm^{-1}): 3386, 3234,

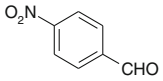
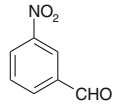
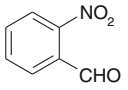
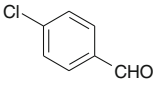
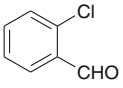
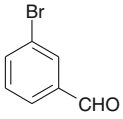
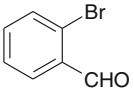
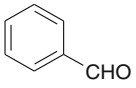
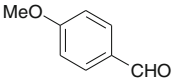
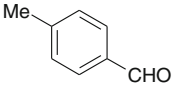
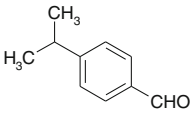
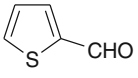
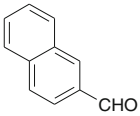
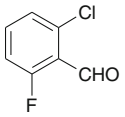
Table 1. Preparation of 1-amidoalkyl-2-naphthol under various conditions.

Solvent	Time/condition	Yield%
$CHCl_3$	24 h/reflux	71
CH_2Cl_2	24 h/reflux	75
MeOH	24 h/reflux	60
EtOH	24 h/reflux	56
DMF	24 h/reflux	15
1,4-Dioxane	24 h/reflux	65
THF	24 h/reflux	61
Solvent-free	7 min/110°C	88

Table 2. Optimization of temperature and amount of boric acid.

Entry	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)
1	10	100	9	78
2	10	110	7	88
3	10	120	5	90
4	10	130	5	86
5	15	120	6	84
6	5	120	4	92

Table 3. Synthesis of 1-amidoalkyl-2-naphthols catalysed by H_3BO_3.

Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P. (°C) (lit. m.p. (°C))[ref]
1		**4a**	4	92	237–238 (237–238)[12]
2		**4b**	4	89	254–256 (256–258)[12]
3		**4c**	6	82	218–219 (218–219)[12]
4		**4d**	5	91	236–238 (237–238)[12]
5		**4e**	7	90	204–205 (206–207)[12]
6		**4f**	7	93	229–230
7		**4g**	10	92	190–191
8		**4h**	6	80	244–245 (245–246)[11]
9		**4i**	12	77	182–183 (183–185)[11]
10		**4j**	10	82	223–225 (224–225)[12]
11		**4k**	12	86	216–218
12		**4l**	10	75	224–225
13		**4m**	9	91	220–222
14		**4n**	10	80	218–219

1638, 1507, 1429, 1091, 807, 740; Anal. Calcd. for $C_{17}H_{15}NO_2S$%: C: 68.66, H: 5.08, N: 4.71, S: 10.78%. Found: C: 68.45, H: 5.26, N: 4.68, S: 10.65%.

2.2d *N-[(2-Hydroxynaphthalen-1-yl)(2-chloro-6-flourophenyl) methyl] acetamide* **(4n)**: White solid; mp 218–219°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.88 (s, 3H), 7.05–7.31 (m, 6H), 7.47 (t, J = 7.2 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 8.59 (d, J = 8.3 Hz, 1H), 9.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9, 45.9, 114.48, 114.72, 115.6, 118.4, 121.8, 122.1, 124.8, 126.4, 127.8, 128.0, 128.1, 128.3, 128.4, 129.4, 132.6, 132.8, 132.9, 153.6, 160.9, 163.4, 168.3 ppm; FT-IR (KBr, cm^{-1}): 3429, 3285, 1644, 1517, 1444, 1102, 813, 775; Anal. Calcd. for $C_{19}H_{15}ClFNO_2$%: C: 66.38, H: 4.40, N: 4.07. Found: C: 66.14, H: 4.54, N: 3.98%.

3. Results and discussion

To optimize the reaction conditions, the reaction of 2-naphthol (1 mmol), 4-nitrobenzaldehyde (1 mmol) and acetamide (1.2 mmol) was selected as a model reaction and carried out in various solvents and under solvent-free condition in the presence of 10 mol% of boric acid. As shown in table 1, higher yield and shorter reaction time was obtained under solvent-free condition.

Furthermore, the model reaction catalysed by 10 mol% of boric acid was studied at different temperatures (table 2, entries 1–4). The reaction rate was increased as the reaction temperature was raised. When it was carried out at 120°C, the maximum yield was obtained in a short reaction period (table 2, entry 3).

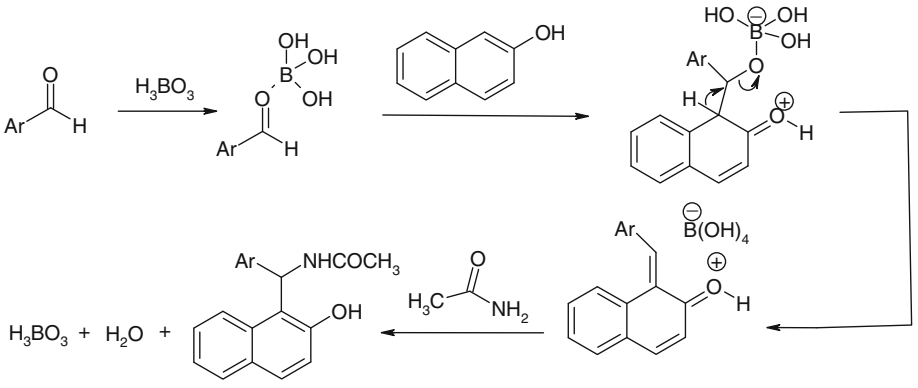
In another study, the condensation reaction of 2-naphthol, 4-nitrobenzaldehyde and acetamide was examined in the presence of different quantities of boric acid at 120°C (table 2, entries 3,5,6). As table 2 indicates, the reasonable result was obtained when the reaction was performed using 5 mol% of boric acid (entry 6). No improvement in the reaction yield was observed by increasing the amount of boric acid to 15 mol% (entry 5).

To demonstrate the scope of the procedure, the condensation of 2-naphthol with various arylaldehydes and acetamide was examined in the presence of boric acid (5 mol%) at 120°C under solvent free condition. The corresponding results are displayed in table 3. As it can be seen in table 3, the reactions were carried out efficiently within 4–12 min and the desired products were produced in good to high yields. The formation of products were confirmed by physical and spectroscopic data and are in good agreement with the reported one.[11,12] Thus, boric acid is an efficient, and mild catalyst for the preparation of 1-amidoalkyl-2-naphthols.

We propose the following mechanism for H_3BO_3 catalysed condensation reaction as shown in scheme 2. The condensation of 2-naphthol, aldehyde and amide may occur by a combined mechanism involving addition, dehydration, and Michael addition. It seems that boric acid increases the electrophilicity of aldehyde considerably.

4. Conclusions

In summary, we have developed very simple, mild, convenient and efficient method for the synthesis of amidoalkyl-2-naphthols by one-pot three-component condensation of aromatic and heteroaromatic aldehydes, 2-naphthol and acetamide using H_3BO_3 as a green catalyst under solvent free condition. The operational simplicity of the procedure, short reaction times, easy workup and environmental friendliness (non-corrosive catalyst) makes this method highly attractive.



Scheme 2. Proposed mechanism for the synthesis of 1-amidoalkyl-2-naphthol.

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